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Postoperative endometrial cancer treatments with electronic brachytherapy source

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Abstract

Purpose: This study is a dosimetric and acute toxicity comparison of endometrial cancer patients treated with either Axxent (Xoft, Inc., San José, CA, USA) electronic and interstitial brachytherapy versus interstitial high dose rate brachytherapy (HDRBT). *Materials and Methods:* Between 2015 and 2017, 94 patients with postoperative endometrial cancer were treated in our centre with the Axxent electronic brachytherapy (eBT) system. The V_{150} and V_{200} are evaluated prospectively for each plan. The mean age of patients was 65.9 years (age range 33–84 years), with different tumour staging. Of the 94 patients, 37 received exclusive adjuvant brachytherapy (25 Gy in five sessions); the remaining patients received external beam radiotherapy (EBRT) with a regimen of 23 sessions of 2 Gy each to the entire pelvis, followed by eBT (15 Gy in three sessions). Additionally, the absorbed doses received by the organs at risk (OAR), urinary bladder, rectum and sigmoid colon were compared with HDRBT plans, evaluating D_{2cc}, $V_{50\%}$ and $V_{35\%}$. Median follow-up was done for each of the 94 patients to assess the toxicity of the treatment: vaginal mucosa toxicity, rectal and urinary toxicity; and results are presented for acute toxicity, toxicity at 1 month after the end of treatment and follow-up after 12 months for a portion of patients according to the Radiation Therapy Oncology Group (RTOG) toxicity criteria. *Results:* The doses in OAR for eBT plans were lower than that for HDRBT plans, both Ir-192 and Co-60 plans, whose doses were similar. The dose in bladder with eBT was 63.8% of the prescribed dose for D_{2cc} versus 70.1% for HDRBT Ir-192, for $V_{50\%}$ was 7.2% versus 12.7% and for $V_{35\%}$ was 15.2% versus 28.2%. In rectum the D_{2cc} was 61.2% versus 68.4%, for $V_{50\%}$ was 7.9% versus 14.3% and for $V_{35\%}$ was 16.7% versus 32%. Results demonstrated lower doses to OAR in all eBT plans. Acute toxicity in eBT was very low in cases of mucositis, with only one case of toxicity greater than grade 1, rectal toxicity and urinary toxicity; results at 1 month are equally good, toxicity symptoms disappeared and no relapses have occurred to date. *Conclusions:* The results of treatment with the Axxent eBT unit for 94 patients are very good, as no recurrence has been observed and the toxicity of the treatment is very low. The increase in V_{150} and V_{200} has not produced an increase in vaginal mucosa toxicity, and the doses in the OAR are lower than in the plans implemented for HDRBT with Ir-192 or Co-60. eBT is a good alternative to treat endometrial cancer in centres without conventional HDR availability. To date, there are limited published studies reporting on outcomes from patients treated with eBT.

Purpose

Electronic brachytherapy (eBT) has been evolving since the turn of the century[1] and has become a treatment option for different types of tumour locations in various scenarios.[2–6] The Axxent eBT unit (Xoft, Inc., an iCAD subsidiary, San José, CA, USA) provides treatment to patients with a 50 kVp miniature X-ray source that directly irradiates the tumour site in skin cancer and with different applicators in the case of breast or gynaecological cancers. This unit allows treatment of skin tumour lesions (nonmelanoma), performance of intraoperative breast radiotherapy and postoperative endometrial and cervical cancer treatments. Specifically, it can also be used to treat local and locally advanced endometrial cancer in protocols that require high absorbed dose rate (HDR) after a hysterectomy and/or external radiotherapy.[7] At our centre, the eBT system was acquired in May 2015 to be used in skin locations and in intraoperative radiotherapy procedures for breast cancer after lumpectomy. From September 2015, postoperative endometrial cancer treatments began and were carried out with Axxent eBT unit. Traditionally, this type of treatment has been carried out in many centres throughout the world with HDR equipment with Iridium-192 (Ir-192, 73.8-day half-life and average energy of 0.355 MeV) sources that irradiate the vaginal vault by a cylindrical

Table 1. Cylinder size and active lengths

d (cm)	Active length (cm)	*n*	%
2.5	2.5	3	3
2.5	3	10	11
2.5	3.5	1	1
3	2.5	5	5
3	3	30	32
3	3.5	3	3
3.5	2.5	3	3
3.5	3	37	39
3.5	3.5	2	2

Abbreviations: *d*: cylinder diameter; *n*: number of patients.

Table 2. Characteristics of electronic brachytherapy sources

Working life of eBT sources	500 min of clinical use
Deviation allowed with respect to calibration certificate	< 10%
Deviation allowed with respect to first measure	< 5%
Maximum energy	50 kVp
Average energy	29.6 keV

Table 3. Patient and treatment characteristics

Patients	94
Age (range, years)	65·9 (33–84)
FIGO stage	
IAG1	4%
IAG2	15%
IAG3	13%
IBG1	15%
IBG2	12%
IBG3	11%
II	12%
IIIA	2%
IIIB	5%
IIIC	11%
IVA	1%
EBRT + eBT	57 patients
Time EBRT to eBT	OTT
14·7 (6–35) days	58·1 (35–78) days
eBT exclusive	37 patients

Notes: Proportions are given with number of total and median range. FIGO stage is given in percentage of the total number of patients.
Abbreviations: eBT, electronic brachytherapy treatment; Time EBRT to BQ, time between the end EBRT and the start of eBT; OTT, overall treatment time; Total time: time from the start of the EBRT to the end of the eBT.

applicator of an appropriate size for each case (generally, the largest size possible, given the patient's anatomy).[8] Other sources have been used for this purpose, such as Cobalt-60 (Co-60, 5.27-year half-life and average energy of 1.25 MeV),[8] with the advantage that there are fewer source changes; therefore, it is more economical, although each brachytherapy session is longer.

Previous published studies for patients treated with Ir-192 compared endometrium,[9,10] cervix[11] and breast,[12] and always showed a lower dose in the organs at risk (OAR) for patients planned with eBT. In all these studies patients were treated with Ir-192, but in our work patients are treated with eBT and we report the monitoring of early toxicity as one of the main objectives of this research.

The aim of this study was to undertake a dosimetric comparison of traditional HDR brachytherapy and eBT to ensure the safety and results in terms of toxicity in OAR. The objective of treatment with eBT is to provide an alternative to the aforementioned radioactive sources with a portable unit, with the resulting advantage of mobility, absence of room shielding (for this energy, an 0.5 mm Pb-equivalent shield in walls and doors is sufficient), avoiding the need to transport and change radioisotope sources and their ease of use.[13]

Materials and Methods

A total of 94 patients were treated with the Axxent eBT unit from September 2015 to October 2017 using cylindrical applicators of sizes ranging from 2.5 to 3.5 cm in diameter, with active lengths of 2.5 to 3.5 cm (Table 1). Each eBT source has a working life of 500 min of clinical use, discounting the quality assurance time; each endometrium session lasted between 3 and 4 min. If a source is not stable or when 500 min of treatment have been reached, it is removed and replaced (Table 2). Ethical approval was gained from Research Ethics Committee of the Autonomous Community of Aragon for the study. The mean age of patients was 65.9 years (33–84 years), with different tumour staging (Table 3). All patients presented with endometrial cancer during this timeframe. Of the 94 patients, 37 received exclusive adjuvant eBT [stage IA cases according to Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) and seven patients with IB1 FIGO stage] (25 Gy in five sessions); the remaining patients received adjuvant external beam radiotherapy (EBRT) with a regimen of 23 sessions of 2 Gy each to the entire pelvis, followed by eBT (15 Gy in three sessions). Sessions were administered twice weekly (Monday and Friday) after EBRT treatment ends. In patients treated with EBRT and eBT, the time from EBRT and the end of eBT is 58.1 days (35–78 days), and the time between the end of radiotherapy and the end of eBT is 14.7 days (6–35 days) (Table 3). Before radiotherapy, 33 patients (35%) received chemotherapy treatment and 61 did not (65%). Calculations made for the patients are compared with the calculations made a posteriori for Ir-192 and Co-60 sources for each of the 94 patients, giving a total of 282 different plans. For eBT, each patient underwent a computed tomography study with sections every 3 mm before the first session. The different OARs of interest were contoured; in this case, the urinary bladder, rectum and sigmoid colon, following the recommendations of the American Brachytherapy Society.[14] Then the planning target

volume (PTV) was contoured and defined by the cylinder along its active length plus a 5 mm margin with the cylinder volume removed from the PTV. The objective is to provide the prescribed dose at 5 mm from the applicator throughout its active length.[14] After the medical physicist prepared the plan, the radiation oncologist approved it, and if appropriate, the patient was treated. Subsequently, two more plans were produced for treatment with Ir-192 and Co-60 sources, respectively.[15–18] The units that we defined in the treatment planning system (TPS) for this purpose are Gammamed Plus (Varian Medical System, Inc.) for the Ir-192 and Eckert & Ziegler Bebig for calculations with Co-60. TG-43 is the algorithm available in our TPS, with which we perform all calculations. In data referring to the PTV, the values of the dose at 90% of the PTV (D_{90}) and of the volume that receives 100% of the dose (V_{100}) have been determined, but will not be shown in this research, as they are the same in the three treatment plans produced, and the same standardisation is implemented in all planning. The V_{150} and V_{200} were also determined. With regard to the OAR, we determined the same parameters for all OAR of interest in the study: urinary bladder, rectum and sigmoid colon. The parameters compared are D_{2cc} (maximum dose at 2 cc of volume), $V_{50\%}$ (volume up to 50% of the prescribed dose) and $V_{35\%}$ (volume up to 35% of the prescribed dose) and assessed toxicity according to the Radiation Therapy Oncology Group (RTOG) parameters.[19]

Results

The mean follow-up of patients was 14 months (4–25). The dosimetry results obtained for patients planned with eBT show much lower doses in OAR than those planned with Ir-192. The mean dose parameters of all treatments compared showed that the bladder D_{2cc} for eBT was 63.8% versus 70.1% for HDRBT Ir-192 with the difference in the $V_{50\%}$ (7.2% versus 12.7%) and $V_{35\%}$ (15.2% versus 28.2%) being much more remarkable.

Also, in the rectum we observed 61.2% versus 68.4% in D_{2cc}, 7.9% versus 14.3% in $V_{50\%}$ and 16.7% versus 32% in $V_{35\%}$. The results for HDRBT Co-60 were similar to those obtained for Ir-192 (Table 4).

The D_{90} of each plan was not included in the results, as it was the value used to standardize each plan. The V_{150} and the V_{200} were higher for cases calculated (and treated) with Axxent than for those calculated with Ir-192 or Co-60, although this difference decreases as the cylinder size increases (Table 5). Acute mucositis cases in patients have not been observed: of the 94 patients treated in our centre, only one presented grade 2 (RTOG) acute toxicity (Table 6).[19] One month after treatment, the patients' vaginal toxicity was grade 0 (RTOG) for 94.7% of the patients and grade 1 for the remaining 5.3%, with grade 2 cases completely disappearing. Rectal toxicity grade 0 was 98.9% and grade 1 was 1.1%, and urinary toxicity grade 0 was 97.9% and grade 1 was 2.1% (Table 7). We observed that patients for whom 12 months have already passed since treatment ended, that is 31 patients, and median follow-up of 19 months (12–25 months) did not present any recurrence. The prescribed dose in each eBT treatment was implemented without considering that we administered treatment with a much lower average beam energy than in the case of Ir-192 (26 keV compared with 355 keV) and therefore, without considering the differences in the different relative radiobiological effectiveness (RBE) expected for low-energy irradiation.[20–22]

Discussion

Results were obtained in patients treated after the first 25 months, with median follow-up of 14 months (4–25 months), on the clinical

Table 4. Mean values of dosimetric parameters

PTV	%(PTV vol.)					
$n = 94$	Axxent 50 kV	SD	Ir-192	SD	Co-60	SD
$V_{150\%}$	**20.1**	6.0	**8.6**	4.9	**7.7**	4.5
$V_{200\%}$	**1.4**	1.5	**0.1**	0.2	**0.1**	0.2
Bladder						
D_{2cc} (%PD)	**63.8**	17.6	**70.1**	14.3	**68.8**	14.1
$V_{50\%}$ (%vol.)	**7.2**	6.6	**12.7**	9.9	**12.0**	10.8
$V_{35\%}$ (%vol.)	**15.2**	12.1	**28.2**	18.7	**26.1**	17.2
Rectum						
D_{2cc} (%PD)	**61.2**	18.3	**68.4**	16.2	**66.9**	15.5
$V_{50\%}$ (%vol.)	**7.9**	6.4	**14.3**	10.8	**12.8**	10.1
$V_{35\%}$ (%vol.)	**16.7**	11.8	**32.0**	19.3	**29.4**	18.1
Sigmoid colon						
D_{2cc} (%PD)	**48.2**	21.3	**57.8**	18.2	**56.2**	18.4
$V_{50\%}$ (%vol.)	**8.6**	10.8	**16.2**	15.9	**15.8**	17.0
$V_{35\%}$ (%vol.)	**21.1**	20.6	**37.4**	23.5	**34.9**	23.7

Abbreviations: PTV, planning target volume; V_{150} and V_{200}, percentage of the PTV receiving 150% and 200% of the prescribed dose; D_{2cc}, maximum dose of 2 cc; %PD, percentage of the prescribed dose; $V_{50\%}$ and $V_{35\%}$, percentage of organ receiving 50% or 35% of the prescribed dose.

Table 5. Mean values per cylinder size

	%PTV vol.	%PTV vol.
$n = 14$		
$d = 2.5$ cm	$V_{150\%}$	$V_{200\%}$
Axxent	22.3	2.1
Ir-192	10.9	0.1
Co-60	10.8	0.1
$n = 38$		
$d = 3$ cm	$V_{150\%}$	$V_{200\%}$
Axxent	19.2	1.8
Ir-192	9.1	0.1
Co-60	6.5	0.0
$n = 42$		
$d = 3.5$ cm	$V_{150\%}$	$V_{200\%}$
Axxent	16.2	0.5
Ir-192	7.1	0.1
Co-60	8.2	0.2

Abbreviations: n, number of patients; d, cylinder diameter; V_{150} and V_{200}: percentage of the PTV receiving 150% and 200% of the prescribed dose.

Table 6. Acute toxicity according to RTOG-EORTC

Acute toxicity						
$n=94$	Grade 0	%	Grade 1	%	Grade 2	%
Acute vaginal mucositis	76	80.8	17	18.1	1	1.1
Acute rectal toxicity	93	98.9	1	1.1	0	0
Acute urinary toxicity	87	92.6	7	7.4	0	0

Note: Grades 0,1,2.[19]
Abbreviation: *n*, number of patients.

Table 7. Toxicity one month after eBT treatment for all 94 patients according to RTOG-EORTC

Toxicity (1 month)						
$n=94$	Grade 0	%	Grade 1	%	Grade 2	%
Vaginal toxicity	89	94.7	5	5.3	0	0
Rectal toxicity	93	98.9	1	1.1	0	0
Urinary toxicity	92	97.9	2	2.1	0	0

Note: Grades 0,1,2.[19]
Abbreviation: *n*: number of patients.

use of the Axxent eBT unit for postoperative treatment of endometrial cancer, indicating why this option is a good alternative.

It is possible to obtain the same vaginal vault coverage as in the planning when using Ir-192 or Co-60, and reduction of doses to OAR is achieved although the V_{150} and the V_{200} of the PTV is increased, which could have produced an increase in acute mucositis cases in our patients but the results of toxicity, together with the dose reduction to OAR, lead us to conclude that eBT is a good alternative to treatments with Ir-192 or Co-60. In another study of only 10 patients treated with Ir-192 and Co-60 and comparing the treatment plans with eBT (10) results reported a difference in rectum for D_{2cc} between eBT and Ir-192 (86.7% versus 88.3% of prescribed dose) but similar results for $V_{35\%}$ (36.9% versus 58.9%) and $V_{50\%}$ (20.4 versus 32.7); for the bladder the D_{2cc} was 43.3% for eBT and 55% of the dosage prescribed for Ir-192 with $V_{35\%}$ (37.9 versus 72.3) and $V_{50\%}$ (15.6 versus 33.9). In a multicentre study of patients treated with eBT,[23] the results are similar to this study: dose to the bladder at $V_{50\%}$ of $11.5 \pm 9.7\%$ and rectum $17.4 \pm 10.9\%$ in eBT plans.

Considering these results, the authors believe that eBT is a good option for a radiation oncology department without a brachytherapy unit (since additional research is needed with longer follow-up) for the treatment of endometrial cancer, given the mobility, versatility and ease of installation of the equipment combined with appropriate dosimetry results and very low toxicity in patients, according to the initial results shown. In the absence of a longer clinical follow-up, the results are highly promising. With regard to the calculation method used, it is recommended[24] to consider the composition of the tissues and perform calculations based on Monte-Carlo models. Our calculations are performed with TG-43 without correction for heterogeneity because it is the algorithm available in our centre and in many other hospitals for which these results will be useful. Although Monte-Carlo methods have been compared with the clinical results of other radionuclides, Reniers et al. came to the conclusion that eBT source has similar RBE as the ^{125}I isotope,[20] for Axxent eBT, the published RBE values are still pending clinical verification.[25] Studies have been done to determine the RBE of 50 keV eBT sources used in this type of treatment, where RBE factors are calculated for different tissues. RBE calculated by Brenner et al. varies between 1.29 and 1.85 with respect to the Ir-192 to 5 mm depth.[21] Publications, after carefully reviewing the prescription of treatments according to these factors,[21,25,26] always recommend that this be done with caution and based on clinical studies; following these recommendations, we should have reduced the prescribed dose to prevent toxicities, and we may have reduced local control. A clinical study showed the reduction of the prescribed dose in the treatment of nodular and superficial basal cell carcinoma, using eBT, based on RBE decreased tumour control from 95 to 90%, showing more tumour control for standard prescription.[27] In reference to the postoperative endometrial cancer treatment, Rava et al. showed a dose decrease in the urinary bladder and rectum, taking into account the equivalent biological dose for an $\alpha/\beta = 3$ (BED3) with eBT, which may be related to a decrease of late toxicity in these organs; all of this was calculated with an RBE factor of 1.5. However, in the same study, there was a dose increase on the surface of the mucosa if we calculate for this same RBE the equivalent doses BED10 and BED3, which would give an overdose to the vaginal vault and higher toxicity of the mucose. Rava et al. suggest considering de-escalation of the dose to account for the differences in RBE,[26] again recommending more clinical studies to consider. Therefore, more studies must be conducted, and more improvements must be made in dosimetry calculation with eBT to compensate for the difference in RBE, although there are important uncertainties in the estimation of this parameter, which imply that the results may vary from one publication to another; it is a subject for discussion.[28] In our case, not using corrections of the RBE has not caused an increase of mucositis or any other toxicity or inadequate local control (only 30 patients had a 12 months follow-up). This study represents the largest published series of patients with endometrial cancer treated with eBT to date, showing excellent results in terms of early effects in all patients with a much lower dose in OAR than in patients treated with sources of Ir-192 or Co-60. Higher values of V_{150} and V_{200} in the case of eBT do not result in higher cases of toxicity to the vaginal mucosa. The dose differences in the OARs are very marked, especially in the $V_{35\%}$ and $V_{50\%}$ are analysed.

Conclusion

The eBT treatments are a great advantage in centres without HDR equipment, although more clinical and local control results with longer follow-up are needed. The eBT equipment is a useful addition to centres with HDR equipment, as a complimentary facility due to its mobility and versatility in being able to perform treatments for endometrial cancer, intraoperative breast radiotherapy, skin cancer and even treatments of cervical cancer in selected cases.

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